66-

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

DOCKET NO.: PMB9658 (ISIS-4502)

PATENT

DECLARATION ACCOMPANYING REPLY
FILED UNDER EXPEDITED PROCEDURE
PURSUANT TO 37 C.F.R. § 1.129

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#81
Plunkett
4/7/03

In re Application of: Tullis	**Confirmation No.: 9155**
Serial No.: 08/078,768	**Group Art Unit: 1631**
Filing Date: June 16, 1993	**Examiner: J. Martinell**

For: Oligonucleotide Therapeutic Agent And Methods Of Making Same

EXPRESS MAIL LABEL NO: EV 160093356 US

Box AF
Assistant Commissioner for Patents
Washington DC 20231

Sir:

DECLARATION OF DR. SIDNEY M. HECHT
PURSUANT TO 37 CFR § 1.132

I, Dr. Sidney M. Hecht, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my knowledge are true and statements made on information or belief are believed to be true. The Exhibits attached hereto are incorporated herein by reference.

2. I am the J.W. Mallet Professor of Chemistry and Professor of Biology at the University of Virginia. I serve as Chairman of the Scientific Advisory Board of Orchid BioSciences, as a member of the Scientific Advisory Boards of Xenogen, Galileo Laboratories and Palumed, and as a consultant for Isis Pharmaceuticals. I am President of Pinnacle Pharmaceuticals and a member of the Board of Directors. I also am a member of the Board of Directors of Orchid BioSciences. I serve as an Associate Editor of the *Journal of the American Chemical Society* and sit on the Editorial Advisory Boards of *Anti-Cancer Drug Design*, *Bioconjugate Chemistry* and *Current Medicinal Chemistry-Anticancer Agents.*

From 1981 to 1987 I held concurrent appointments at Smith Kline & French Laboratories, first as Vice President Preclinical R&D, then as Vice President Chemical R&D. I have been an Alfred P. Sloan Fellow and a John Simon Guggenheim Fellow at the Max Planck Institut für Experimentelle Medizin at Göttingen. In 1991 I served as a Professor Associé at the Muséum National d'Histoire Naturelle in Paris and Gastprofessor at the Eidgenössische Technische Hochschule in Zürich; I studied at the Museum again for six months during 2000. I have held numerous lectureships at other universities. I received the 1996 Cope Scholar Award of the American Chemical Society and was selected as Virginia's Outstanding Scientist for 1996. More recently I received the 1998 Research Achievement Award of the American Society of Pharmacognosy.

A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. As early as 1969, I studied mechanisms of protein synthesis via gene expression and regulation thereof. As early as 1972, I co-authored scientific journal articles regarding these studies. Further I have studied the chemistry and biochemistry of nucleic acids since 1966.

My decades of experience as a biological chemist have instilled in me a knowledge of mechanisms of expression of specific genes.

4. I have read and am familiar with the contents of the above-referenced patent application. I have read and agree with the declarations of Dr. Jerry L. Ruth, Dr. Dennis H. Schwartz, and Dr. Stanley T. Crooke previously submitted in connection with the present application. I further understand that the nature of the rejection at issue in the pending application is that the Examiner believes that the pending claims are overbroad in view of the skepticism of critics of antisense technology between October 1981 and the present. It is asserted by the Examiner that the time lapse between October 1981 and the dates of publication of the numerous references cited by the Applicant to support his claim that the methods of the invention work as set forth in the application weighs heavily against the assertion that the instant application provides sufficient guidance to one of skill in the art to practice the claimed invention as early as October 1981. The purpose of this declaration is to address this issue.

I will explain that the concerns of the Examiner stemming from a review of articles by antisense critics including Gura, Rojanasakul, and Hijiya are directed to the immediate clinical applicability of antisense applications rather than to the efficacy of *in vivo* antisense technology applications and, in any event, that those concerns have been proven baseless. I will explain why a significant delay in the reporting of clinical results is routine in the field of drug discovery and development. I also will explain that the numerous clinical investigations conducted on *in vivo* antisense methodologies demonstrate the confidence of pharmaceutical companies and, hence, those skilled scientists who comprise them in the use of antisense technology *in vivo* as detailed by the present application.

In short, the opinions of naysayers that have been lodged against the validity of antisense technology were wrong when made and have been proven to be wrong. Antisense technology works *in vivo* in accordance with the principles of the present invention. The invention as set forth in the application and as presently claimed has been proven to work time and again in the years following the effective filing date of the present application. No further disclosure than that made by Applicant in 1981 was necessary to practice the invention as presently claimed. Applicant was absolutely correct in 1981 and has been proven correct repeatedly thereafter. Additionally, a significant delay in the reporting of clinical results is routine in the field of drug discovery and development, particularly in the present case, where antisense technology was developed by small pioneer companies. The large investments by pharmaceutical companies in the development of antisense technologies underscores their belief in the efficacy of *in vivo* antisense applications. Their continued investments and positive results prove the continued vitality of that belief.

5. Any concerns raised by Gura (*Science*, 270: 575-577 (1995)), Rojanasakul (*Adv. Drug Delivery Revs.*, 18: 115-131 (1996)), and Hijiya (*PNAS USA*, 91:4499-4503 (1994)) are directed toward the immediate clinical applicability of *in vivo* use of antisense technology. These authors do not question the efficacy of antisense applications *in vivo*. For example, Rojanasakul at page 118 queries "Can antisense work in living systems?" and responds by stating that while "there are studies which indicate the ***relative safety*** of antisense [oligonucleotides] *in vivo* . . . ***non-specific side effects*** of [antisense oligonucleotides] have also been reported in mice." Rojanasakul goes on to say that these safety concerns "do not diminish the potential use of [antisense oligonucleotides] *in vivo*, and there are few examples of successful *in vivo* treatment in the absence of specialized delivery systems." *Id.*

Rojanasakul continues, stating that "[c]onsidering the various obstacles that the antisense [oligonucleotides] must encounter prior to their action . . . ***the desired activity of [antisense oligonucleotides] is observed.***" *Id.* (emphasis added).

Gura, a non-research-performing reporter, avers that "some experts in the field . . . argue that clinical trials have begun far too soon." Gura at 575. Such concerns regarding the clinical safety of antisense oligonucleotides were elicited by the side effects detected in some animal studies. For example, Gura describes one set of experiments in which lethality in monkeys administered a one-time, high-dose injection occurred as well as another set of experiments in which a transient decrease in two kinds of white blood cells and changes in heart rate and blood pressure resulted from the high dose administered. *See id.* at 576.

Similarly, the assertion that Hijiya characterizes the field of antisense as being "in its scientific infancy" is misplaced. Hijiya makes clear that antisense oligonucleotides worked therein: "The experiments reported herein serve as a paradigm of [oligodeoxynucleotide]-based therapeutics for human malignancies." Hijiya at 4503. Hijiya reasons that, although *MYB* (a gene) is an effective target of antisense oligonucleotides in human melanoma, "further development of the antisense strategy will be needed before the successful application of this technique ***in the clinic*** can be anticipated." *Id.*

"No drug is free of toxic effects." *See* Fingl and Dixon (Chapter One, "General Principles", In THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 4th edition, L.S. Goodman and A. Gilman, Eds. (1970)) (Exhibit 2). This fact has been known for many years and is as true today as it was when first presented in this textbook. For some authors, to question the clinical safety of a new drug paradigm is not surprising. If raising such questions were to bar patentability of new drugs, there would be no new drugs. Accordingly, some toxic effects of

antisense therapeutics are to be expected. Some expected toxic effects, however, are not an indication that antisense therapeutics do not work *in vivo*.

Moreover, any concerns voiced by Gura, Rojanasakul, and Hijiya regarding the use of antisense technology *in vivo* have been proven to be wrong. The successes achieved in the field of antisense technology have been witnessed, thereby ratifying the views of proponents of antisense at the time of the invention and silencing, indeed converting, many critics to what is clearly the correct view: antisense works *in vivo* as taught by the present application.

A number of articles that corroborate the *in vivo* success of antisense technology have been cited during prosecution of the present application. Further submitted with the accompanying reply is Mirabelli et al. (*Anti-Cancer Drug Design*, 6:647-661 (1991)) (Exhibit 3) which notes that antisense oligonucleotides have demonstrated activities against a broad array of targets, that "the therapeutic indexes of phosphorothioate oligonucleotides appear to be quite high," and that "certain phosphorothioates . . . are extremely well tolerated in animals." Mirabelli at 651. Mirabelli also provides evidence of successful *in vivo* trials of antisense oligonucleotides. *See, e.g.,* Mirabelli at 653.

Crooke (Annu. Rev. Pharmcol. Toxicol., 1992, 32:329-76) (Exhibit 4) corroborates the *in vivo* stability of antisense oligonucleotides, noting that nuclease activity of sera derived from different species varies, with human being the least active. *See, e.g.,* Crooke 1992 at 337. Additionally, modified oligonucleotides enter cells at pharmacologically relevant concentrations. *See id.* at 338-339. *In vivo* pharmacokinetic studies reveal that antisense oligonucleotides are rapidly and broadly distributed following administration in mice, rabbits, and rats. *See id.* at 342-343. Toxicity studies reveal that phosphorothioate oligonucleotides,

for example, have high therapeutic indices and exhibit toxicity only at concentrations far in excess of concentrations at which therapeutic activity is observed. *See id.* at 344; 346-347.

Cossum (*J. Pharm. and Exp. Ther.*, 267(3):1181-1190 (1993)) (Exhibit 5) describes several *in vivo* studies in which phosphorothioate oligonucleotides were shown to be widely distributed following *in vivo* administration in nothing more than phosphate buffer at physiologic pH. *See, e.g.,* Cossum at 1181-1182, 1186. Additionally, Cossum acknowledges that the dosages at which non-antisense effects occur are significantly greater than those at which antisense effects are observed. *See id.* at 1181.

Stepkowski et al. (*J. Immunol.*, 153:5336-5346 (1994)) (Exhibit 6) demonstrates specific inhibition of intercellular adhesion molecule-1 (ICAM-1) expression by antisense molecule IP-3082, thereby promoting heart allograft survival. *See* Stepkowski et al. at 5338. Extension of *in vitro* studies to *in vivo* analyses confirmed the correlation between the efficacy of antisense technology in a Petri dish and in a living organism.

Indeed, a search of the art of "antisense" in the PubMed database reveals approximately 16,986 references demonstrating the extensive interest of the scientific community in the technology of the presently claimed invention (Exhibit 7).

6. The Examiner asserts that the time lapse between the effective filing date of the present application and the numerous references cited in support of enablement of the solicited claims weighs heavily against the claim that the instant application provides sufficient guidance to one of skill in the art to practice the claimed invention as early as the effective filing date of the instant application. I disagree. Had the pharmaceutical industry in 1981 immediately applied its existing knowledge of medicinal chemistry and pharmacology to the teachings of Applicant, I believe that it would have practiced the present invention.

Various factors contributed to this lag, not the least of which include establishment, within an organization, of an internal "champion" for a new technology paradigm where the champion is willing to sponsor and defend reallocation of resources from existing programs to new a program. Also, once acceptance of the new paradigm is made, established pharmaceutical practice requires pharmacologists to perform substantial and numerous pre-clinical studies to determine the toxicological profile, pharmacokinetics, and pharmacodynamics of any potential drug. Thus, my extensive experience as a biological and medicinal chemist have taught me that it is not unexpected that the generation and reporting of pre-clinical and clinical studies by the pharmaceutical industry related to the efficacy of a potential drug does not immediately follow the publication of the first few positive *in vitro* results.

It has been observed by Fingl and Dixon (*see supra*, paragraph 5) that "[n]o drug is free of toxic effects." They further state, however, that "adverse effects do not arise solely because of the inherent toxicity of drugs and the limitations of the methods for early detection of this toxicity. *Many of the adverse effects could be avoided if drugs were used more carefully and more wisely.*" *Id.* at 26 (emphasis added). Further, "[t]he development and evaluation of new drugs in the United States is rigidly controlled by federal regulation administered by the Food and Drug Administration. A new drug may not be marketed for general clinical use until it has been subjected to thorough clinical pharmacological studies and until 'substantial evidence' of its efficacy and safety have been obtained from adequate, well-controlled clinical trials conducted by qualified investigators." *Id.* at 29.

Since both positive and negative results must be included in data packages submitted to regulatory agencies, clinical trials are not performed haphazardly with selective omission of negative results. In other words, slapdash animal studies are not conducted for potential

human therapeutic applications because all data collected is subjected to FDA scrutiny. Accordingly, every study is implemented pursuant to highly rigorous standards and carefully planned conditions. Animal tests suitable to regulatory agency submission require established animal colonies and adequate animal care facilities with appropriate veterinary oversight, the development of which is expensive and time-consuming. Accordingly, careful animal experiments do not yield large volumes of publications that appear in the literature quickly. They require systematic studies that may take years to accomplish. In other words, a significant delay in the reporting of pre-clinical or clinical results is entirely routine in the field of drug discovery and development.

While contributing early-published papers related to *in vitro* related research topics, individual academic researchers, who contribute much of the scientific literature, did not exploit and publish, *in vivo* antisense technology. The reasons for this are varied. The very substantial costs of animal studies, resulting from the necessity of numerous controls as well as the stringent regulations imposed by academic institutions and regulatory agencies, preclude most academic researchers from pursuing such studies absent industrial sponsorship. Additionally, the experiments conducted by most academicians are limited in scope to their existing, well-delineated areas of research interest. Accordingly, academic researchers do not perform isolated experiments that have no bearing on that research interest. Rather, academics are selective in choosing the focus of their experiments, limiting their experimental objectives to the particular area of research that fits into the grand scheme of the research to which their careers are dedicated, for which they have received institutional approval to study, and for which they have been granted funding.

7. The numerous clinical investigations conducted and patents sought on *in vivo* antisense methodologies demonstrate the confidence of pharmaceutical companies and, hence, the skilled scientists that comprise them in the use of antisense technology *in vivo* as detailed by the present application. "Big" pharmaceutical companies became interested in antisense technology after the small pioneer companies confirmed its validity. For example, pioneer companies Hybridon Inc. and Isis Pharmaceuticals, Inc. were incorporated in 1989 for the purpose of developing antisense therapeutics. Gilead Sciences, Inc. formed in 1987 for the same purpose. Genta Inc. was established as a spin-off of Gen-Probe in 1988 with a business objective of developing antisense therapies initiated in Gen-Probe's diagnostic antisense studies. In the mid- and late 1990s, newcomers MethylGene Inc., Inex Pharmaceuticals Corp., and NeoPharma, to name only a few, joined the early-stage companies in exploiting the therapeutic aspects of antisense technology.

In short, antisense technology was developed by small, early stage companies having limited resources. In view of the need of such companies to conserve their limited resources and the knowledge of such companies that a single poorly planned trial yielding a negative outcome could devastate an entire business venture, the pioneer companies in the antisense field had every incentive to perform animal trials carefully and systematically. They conducted animal trials in a highly methodical manner and at timepoints dictated by scientific and business judgment to advance to that phase in the process of moving their drug candidates toward IND status. Pharmaceutical companies including Isis Pharmaceuticals, Genta Inc. and Hybridon Inc. and their present or past large pharma partners including Novartis, Lilly, Abbott, Merck, Aventis, Amgen, Roche and Boehringer Ingelheim have invested huge amounts of time and money to verify the efficacy of antisense drugs in an

effort to propel them through clinical phases and into the market. Given the enormous costs associated with drug development and marketing, pharmaceutical companies would not have invested so heavily in the development of antisense technologies if they believed antisense molecules would not work *in vivo*.

8. In summary, the opinions of naysayers that have been lodged against the validity of antisense technology were wrong when made and have been proven to be wrong. Antisense technology works *in vivo* in accordance with the principles of the present invention. The invention as set forth in the application and as presently claimed has been proven to work time and again in the years following the effective filing date of the present application. No further disclosure than that made by Applicant in 1981 was necessary to practice the invention as presently claimed. Applicant was absolutely correct in 1981 and has been proven correct repeatedly thereafter. Additionally, a significant delay in the reporting of clinical results is routine in the field of drug discovery and development, particularly in the present case, where antisense technology was developed by small pioneer companies. The large investments by pharmaceutical companies in the development of antisense technologies underscores their belief in the efficacy of *in vivo* antisense applications. Their continued investments and positive results prove the continued vitality of that belief.

Date: 03/04/03

Dr. Sidney M. Hecht

Attachment
Exhibits 1, 2, 3, 4, 5, 6 and 7